REMARKS

Claim 68 has been amended for clarity and to correct the misprint of "X^5" to insert the unintentionally omitted definition of X^4. Support for this definition is found in the dependence of claim 68 on claim 61. The resulting nature of X^4 is also explained in Table 1 on page 36 of the Response to the Restriction Requirement. A copy of this explanation is attached as Exhibit A for the convenience of the Office.

Claim 68 has also been amended to change the word "restrictions" to "characteristics." Applicants understand that, in view of the discussion at the interview, this amendment to claim 68 places it in a position for allowance along with the claims dependent thereon, claims 69-74. It is believed that claim 75, also dependent on claim 68, is in a position for allowance as well; it is unclear why the Office would consider this claim as a separate invention, as further discussed below.

Claim 61 has been amended to clarify that it is, indeed, restricted to the core structure of the elected invention. This was the intent of the original claim, as noted by the requirement that it is a modified 6-dEB synthase. However, it has now been clarified that the 6-dEB synthase contains all the modules of the synthase and that the polyketide that results has the ring carbon skeleton of 6-dEB. The terminology has also been corrected to change "macrolide" to "polyketide." No new matter has been added by this amendment; it is for clarification only.

Entry of the amendment is therefore respectfully requested.

The Invention

The invention resides in applicants' ability to modify the beta-keto modifying (BKM) catalytic region in modular polyketide synthases so that additional modifications occur to the keto

groups originally present in the condensed polyketide chain. Specifically, the claims are directed to polyketides or glycosylated polyketides that are obtainable by making this kind of modification. In reality, the scope of claim 61 is highly similar to that of claim 68, but expressed in product-by-process terms so that the unifying concept becomes clear. As will be shown below, the documents cited by the Office do not disclose products of PKS with such modifications.

In this regard, it appeared from the discussion at the interview that the Office was not convinced that claims 61-67 were actually product claims. Although the product is described in terms of the method of its preparation, this method is sufficiently definite that the nature of the product is clear. The process involves synthesizing a polyketide using a polyketide synthase that is a complete 6-dEB synthase that will result in the ring structure shown in claim 68. Because at least one of the modifications in a)-d) is required in the complete 6-dEB synthase, one of the characteristics specifically required in claim 68 must automatically result. Thus, claim 61 is only slightly broader than claim 68 in that there may be additional modifications which still require a complete 6-dEB synthase, such as modifying an acyl transferase (AT) region. This would result in the possibility that R′ and R^1-R^6 might be other than methyl. However, these modifications are not required. Applicants believe, therefore, that claim 68 is a species of claim 61.

The Withdrawn Claims

Claims 61-67 were withdrawn from consideration as assertedly extending beyond the elected invention. It is believed that the amendment to claim 61 clarifies that, for example, the compounds in restricted groups XXIV or XXV are not included. In view of this amendment, it is respectfully submitted that consideration of claims 61-67 in this application is proper. Applicants again note

that claims 61-67 are drawn to products, not to methods of preparation. The method of preparation is merely set forth as an alternative method of describing the product.

The Species Election

Applicants are unclear as to whether their species election is objected to. A specific compound, 11-deoxy-6-dEB, has been elected. Applicants understand that claim 75 is directed to a non-elected species; however, there is a linking claim - claim 68, which includes both the elected and non-elected species. Therefore, consideration of claim 75 in this application is also believed proper.

Priority

Applicants believe the Office is in error in according the present application a priority date only of 6 May 1998. While the parent application, U.S. 08/846,247 filed 30 April 1997, may not disclose the compound of claim 68 *in haec verba*, clearly the disclosure of the '247 application constitutes an enabling written description of the invention as claimed. *In haec verba* disclosure is not required. See *Kennecott Corp. v. Kyocera Int'l, Inc.*, 835 F2d 1419, 5 USPQ2d 1194 (Fed. Cir. 1987). As seen from the structure in claim 68, the claimed compounds are those that result from substituting a corresponding beta-keto modulating (BKM) region which contains at least one *additional* catalytic activity in an erythromycin polyketide synthase. This is clearly disclosed in the parent application. For example, the claims themselves are directed to a method to prepare a nucleotide sequence encoding a modified PKS by, according to claim 3, replacing one region in the cluster with a region encoding the corresponding enzymatic activity from a different naturally occurring PKS gene or from a different region of the same naturally occurring PKS gene. It is made clear, on page 11, that a complete reductase cycle corresponding to KR/DH/ER would correspond to

KR alone. Preparation of representative compounds of this type is described, for example, on page 24 in Table 2, as the Examiner recognizes. Thus, while the parent application does not specifically show the structure of the resulting polyketide when the manipulations described are carried out, the parent clearly teaches providing polyketide synthases with the modification in at least one BKM region in erythromycin PKS as required by the present claims, to result in the polyketides claimed in claim 68. Reference to claim 61, which applicants believe is properly considered in the present prosecution, makes this even more clear. Accordingly, applicants believe that they are entitled to benefit of the 30 April 1997 date. Applicants do not agree that the genus of claim 68 is not disclosed in the parent application; while all individual species of this genus are not each particularly described, the genus itself is described.

In any case, because the outstanding rejections can be addressed without reference to the appropriate priority, this issue is at present moot.

Formal Matters

Applicants appreciate the consideration of the Information Disclosure Statements filed 29 April 2002 and 25 August 2003. A correction to the specification on page 2, line 4, as requested, was submitted to the Office in the Response to an Office action which Response was filed 17 October 2003.

In view of the amendment to claim 61, applicants believe its maintenance in the application is proper. Therefore, claims 68-74 are properly dependent.

The Rejection Under 35 U.S.C. § 112, Paragraph 1

The Office objects to claims 68-74 of the present application as putatively comprising new matter. The Office refers to claim 68 and states that there is no support for the possibility that X^3 is either H or OH or for the embodiment wherein X^4 is H or the embodiment wherein X^2 is OH.

Applicants wish to call the attention of the Office to page 22 of the specification which depicts the formula set forth in the claims. According to the description, each of X^1-X^5 may be H_2, HOH, or =O. Therefore, if the undepicted substituent in the present formula is H, it is clear that X^3 can be H or OH (*i.e.*, X^3 can be H_2 or HOH), X^4 can be H (*i.e.*, X^4 is H_2), and X^2 can be OH (*i.e.*, X^2 is HOH). The formula on page 22 simply differs in that X^1-X^5 are described in terms of both substituents attached to the ring position, rather than being described only as one of the two possibilities in the claims (the other substituent being understood as H). Indeed, X^3 is shown as OH in structures 11-21 and 11-22 in the parent application.

Thus, the claim is fully supported in the application as filed and withdrawal of this rejection is respectfully requested. Applicants understand, from the discussion at the interview, that the foregoing explanation is adequate to demonstrate support for the present claim language.

The Rejection Under 35 U.S.C. § 112, Paragraph 2

First, the terminology "and/or" is objected to. While applicants believe no unclarity results from this terminology, it has been deleted from the claim as unnecessary. The Office also states that claim does not define X^4 if a pi bond is not present; applicants appreciate this oversight being pointed out and the oversight has been corrected by amendment.

Applicants do not understand the objection to "process limitations" in claims 69-74. These are not process limitations but the "restrictions" set forth in claim 68 "wherein at least one of the

following *restrictions* is present." Moreover, for clarity, "restrictions" has been changed to "characteristics." Thus, this rejection may be withdrawn.

The Art Rejections

Claims 68-74 were rejected as assertedly anticipated by U.S. patent 6,060,234 (Katz) on the basis that the compounds disclosed therein anticipate the claimed compounds.

Respectfully, applicants believe that the Office has misread the Katz patent.

The compounds of the Katz patent are listed in Table 1, starting at columns 19-20. In these compounds, the corresponding position to X^1 is always OH; the position corresponding to X^2 is always =O; the position corresponding to X^3 is always OH or O-desosamine; the position corresponding to X^4 is always OH or O-cladinose, so X^1 is never H, X^2 is never OH or H, X^3 is never H, and X^4 is never H. There are no pi bonds in the structure at the positions indicated in the present claims. Therefore, none of the compounds of the Katz patent contain "at least one of the characteristics" required in the present claims.

Similarly, the rejection over U.S. patent 6,033,883 (Barr) overlooks the absence of these characteristics in the disclosed compounds, in particular 6-dEB shown in Figure 2. Clearly none of the restrictions: X^1 is H, X^2 is H or OH, X^3 is H, X^4 is H or a double bond is present, applies.

The reason that none of the "characteristics" is present in the cited documents is that neither Katz nor Barr teach the type of modification in the polyketide synthase necessary to result in these restrictions in an enabling manner. Clearly Barr is unconcerned with any modifications to the modular PKS which would result in altered products. While Katz is concerned with modifications to a PKS, none of the compounds shown in the Katz patent show the result of such modifications. The distinction between products and methods is important, as Katz does propose a method to direct

the synthesis of an erythromycin by genetic manipulation of the gene encoding the deoxyerythronolide B synthase function of an erythromycin producing organism. Claim 1 of U.S. 5,824,513 to Katz, *et al.,* which is of record, is directed to such a method. Claim 6, dependent thereon, suggests that one or more additional domains provide an enzymatic activity affecting the processing of β carbonyl groups selected from β-keto reductase, β-keto reductase and dehydratase, and β-keto reductase, dehydratase and enoyl reductase be provided. No specifics with regard to modules are given, nor did the Katz patent as filed describe the location of the β-keto modifying regions of the 6-dEB synthase; instead, such information was provided by a sequence listing submitted after the patent application was filed. Thus, Katz does not describe the products claimed in claim 61 or claim 68 or an enabling method for obtaining such products.

Thus, the claims as amended are not anticipated and are not suggested by the cited documents.

Double-Patenting

Claims 68-74 were rejected as obviousness-type double-patenting over claims 1-53 of U.S. patent 6,558,942. A terminal disclaimer with respect to this patent is submitted herewith thus obviating this basis for rejection.

CONCLUSION

The claims have been amended for clarification and to resolve certain formal matters: It has been shown that the cited documents do not describe or suggest the inventive modifications of the PKS modules as claimed in the present application. A terminal disclaimer has been submitted to obviate the rejection for double-patenting. Accordingly, it is believed that claims 61-75 are in a position for allowance and passage of these claims to issue is respectfully requested.

If it is considered that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 300622000501.

Dated: May 12, 2004

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It should be appreciated that

1) the stereochemistry of the claimed macrolide is identical to the stereochemistry shown in present claim 29;

2) The definitions of R^1-R^6 are within the scope of claim 29--they are all methyl groups because of the nature of the extender unit accepted by the modules of erythromycin PKS, and no modifications are required of the AT catalytic domains which control the nature of the extender units employed;

3) R^* is consistent with the natural starter units employed by the erythromycin PKS.

All of the compounds within the scope of the invention are the result of at least one modification of a BKM region of the erythromycin PKS to contain at least on additional catalytic activity as stated above. The following table is intended to elucidate the nature of these modifications.

Table 1

POSITION	CONTROLLED BY MODULE	CATALYTIC ACTIVITY	EMBODIMENTS OF X
13	1	KR	—
11	2	KR	X^1 is OH or H
9	3	—	X^2 is =O or OH or H
7	4	KR/DH/ER	—
5	5	KR	X^3 is OH or H
3	6	KR	X^4 is OH or H

Table 1, in the left-hand column, shows the position in the formula of claim 68 whose oxidation state will be controlled by the modification of the relevant BKM region. The second column lists the module in which the relevant BKM module resides. The third column lists the character of the BKM region in the native module — *i.e.*, the catalytic activities present. As seen,